UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/766,642	01/28/2004	Anthony Atala	105447-2	4621

21125 7590 01/27/2005

NUTTER MCCLENNEN & FISH LLP
WORLD TRADE CENTER WEST
155 SEAPORT BOULEVARD
BOSTON, MA 02210-2604

EXAMINER	
FORD, ALLISON M	
ART UNIT	**PAPER NUMBER**
1651	

DATE MAILED: 01/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	10/766,642	ATALA ET AL.
	Examiner	Art Unit
	Allison M Ford	1651

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *14-22 and 30-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 23-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-32* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-13 and 23-29, drawn to a method of organ augmentation, classified in class 435, subclass 373.

II. Claims 14-22 and 30-32, drawn to a method of tissue repair, classified in class 435, subclass 377.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are distinct inventions and thus are subject to restriction. The inventions are distinct processes in that the methods are not dependent on each other, not to be used together and have different functions, modes of operation, and effects. In the instant case the method of Invention I requires the co-administration of a second population of non-transfected cells, which is not required in the method of Invention II. Additionally, the method of Invention II requires screening of the transfected cells for expression of an appropriate isolate, which is not required in the method of Invention I.

Therefore, a search and examination of all inventions in one patent application would result in an undue burden. These inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, different classifications, and a search for one group does not require a search for another group, restriction for examination purposes as indicated is proper.

During a telephone conversation with Mr. Engellenner on 1/4/05 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-13 and 23-29. Affirmation of this election

must be made by applicant in replying to this Office action. Claims 14-22 and 30-32 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Priority

Acknowledgement is made of applicant's claim for priority to provisional application 60/443,129, filed 1/28/2003.

Claim Rejections - 35 USC § 112

Claim1, 3-13 and 23-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant clearly submits in the specification that the chronic expression of angiogenesis modulating agents, such as VEGF, is detrimental to the tissue by causing vascular abnormalities (See specification, Pg. 29). For example, Lee et al describes vascular tumors and hemangiomas resulting from implantation of VEGF-expressing myoblasts into non-ischemic muscle (See Lee et al, Pg. 899, col. 2-900, col. 1). Lee et al attribute the lethal results to over vasculogenesis due to the concentrated, chronic over expression of the VEGF. Similar results and conclusions were made by Springer et al (Molecular Cell, 1998, See pg. 549, col. 2). Therefore one of ordinary skill in the art is not enabled to augment the organs if the dosage of VEGF is lethal; rather one would have to transiently transfect the population of cells with a plasmid that encodes for the angiogenesis modulating agent so that the VEGF, or other angiogenesis modulating agent is expressed transiently.

Accordingly, because transient expression of angiogenesis modulating agents is required to allow for successful, viable, augmentation of organ function, as discussed above, one would have to chose

transfected cells that would only transiently express the angiogenesis modulating agent, therefore stably transfected cells would not be suitable for use in the method. Thus, the requirement of claim 10, wherein the step of transfecting cells comprises selecting stably transfected cells, does not enable the method of augmenting organ function, for the reasons discussed above, namely that it would cause the deleterious effects to the host organism.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5-7 and 23-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's claim 5 requires the method of claim 1 to further comprise co-administering a second population of cells. Claim 6 requires the second population of cells to comprise undifferentiated cells. Claim 7 requires the second population of cells to comprise vascular endothelial cells. Claims 23-29 also require one cell population to be transfected with a plasmid encoding for an angiogenesis modulating agent and co-culturing the transfected cell population with a second cell population. However, it is not clear if the second cell population (the non-transfected cell population), in either method, effects the augmentation of the organ function, as it does not appear to have an integral role in the method.

Applicant's claim 23 is directed to a method for augmenting organ function comprising: culturing at least one population of cells on a matrix material to produce an organ construct capable of differentiating *in vivo* to replace or augment organ function; transfecting a second population of cells with a plasmid encoding an angiogenesis modulating agent; and implanting the organ construct and the transfected cells *in vivo* at a target site. However, it is not clear if it is required that the organ construct

and the transfected cells be implanted at the same target site *in vivo*, or if they have any interaction at all *in vivo*. Claims 24-28 have the limitation of claim 23, and thus are rejected on the same basis.

Additionally, claim 27 recites the limitation "the cells," it is not clear which cells are being referenced, the initial population that is to be cultured on the matrix, or the second population that is to be transfected, or both.

Claim 29 recites the limitation "the tissue layer" in the first line of the claim. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 5, 6, 8, 10, 11 and 13 are rejected under 35 U.S.C. 102(a) as being anticipated by Schuch et al (Blood, Dec 2002).

Applicant's claim 1 is directed to a method of organ augmentation comprising the steps of: transfecting a population of cells with a plasmid encoding an angiogenesis modulating agent; and implanting the transfected cells into a target tissue region where the cells will express the angiogenesis modulating agent thereby inducing assimilation and differentiation of cells in the target region. Claim 5 requires the method to comprise co-administering a second population of cells. Claim 6 requires the second population of cells to be undifferentiated cells. Claim 8 requires the cells to be suspended in a

pharmaceutically acceptable carrier. Claim 10 requires the pharmaceutically acceptable carrier to comprise a polymer matrix. Claim 11 requires the step of transfecting the cells to further comprise selecting stably transfected cells. Claim 13 requires the angiogenesis modulating agent to be VEGF.

Schuch et al teach a method of organ augmentation comprising transfecting a population of normal murine mammary gland (NMuMG) endothelial cells with a plasmid encoding a $VEGF_{165}$ gene, cells were encapsulated in a polymer matrix comprised of poly-L-lysine (a pharmaceutically acceptable carrier), encapsulated cells were then co-administered with M1 cells (murine leukemic myeloblasts, an undifferentiated myelocyte precursor) subcutaneously to SCID mice (See ATCC Catalog Detail & Schuch Pg. 4623 and Pg. 4626, col. 2) (Claims 1, 5, 6, 8, 10, 11 & 13). Tumors exposed to the constant release of $VEGF_{165}$ showed an accelerated growth compared to non-VEGF-exposed tumors; therefore the VEGF induced assimilation and differentiation of cells in the target region (See Pg. 4624, col. 2) (Claim 1). Therefore the reference anticipates the claimed subject matter.

Claims 1, 8 and 13 are rejected under 35 U.S.C. 102(b) for being anticipated by Parmacek et al (US Patent 6,297,221).

Applicant's claim 1 is directed to a method of organ augmentation comprising the steps of: transfecting a population of cells with a plasmid encoding an angiogenesis modulating agent; and implanting the transfected cells into a target tissue region where the cells will express the angiogenesis modulating agent thereby inducing assimilation and differentiation of cells in the target region. Claim 8 requires the cells to be suspended in a pharmaceutically acceptable carrier. Claim 13 requires the angiogenesis modulating agent to be VEGF.

Parmacek et al teach a method of organ augmentation comprising transfecting a population of vascular smooth muscle cells with a plasmid encoding VEGF, an angiogenesis modulating agent, ex-vivo; and then implanting the transfected VSMCs into a subject (See col. 7, ln 52-67) (Claims 1 & 13).

Parmacek et al further teach that the transfected VSMCs onto a bioprosthetic graft or stent (which applicant calls a pharmaceutically acceptable carrier) (See col. 8, ln 1-6) (Claim 8). Therefore the reference anticipates the claimed subject matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-10, 23, 24-25 & 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Atala et al (US Patent 6,479,064), in view of Yla et al (Lancet, 2000), further in view of Cima et al (J. Biomed Engineering, 1991) and Griffith-Cima (US Patent 5,709,854).

Atala et al teach a method of augmenting organ function comprising culturing a population of endothelial cells on a three-dimensional matrix to form an organ construct capable of differentiation *in vivo* to replace or augment organ function; and seeding a second population of parenchymal cells onto the matrix; and co-administering the cell populations by implanting the organ construct *in vivo* at a target site to induce assimilation and differentiation of cells in the target region (See col. 2, ln 19-52; col. 12, ln 37-49; and Claims 1 & 14) (Claims 1, 5, 23 and 29). Atala et al teach the endothelial cells to form a primitive vascular system, therefore it appears Atala et al intends to use vascular endothelial cells (See col. 2, ln 19-52) (Claims 4 and 7); the parenchymal cells can comprise undifferentiated muscle stem cells (See col. 9, ln 7-19) (Claims 3 and 6). Atala et al teach either the endothelial cells or the parenchymal cells can be transfected, by any means known in the art, to produce a gene product beneficial for transplantation, such as angiogenesis modulating agents IL-1 or IL-2 (See Specification, Pg. 3; See Atala

et al col. 10, ln 4-23 & col. 14, ln 24-30). The three-dimensional matrix can be implanted into the subject, therefore it acts as a pharmaceutically acceptable carrier; it can comprise decellularized tissue, it can further be treated with collagen or other materials to aid in cellular attachment and growth (See col. 11, ln 30-38 & col. 12, ln 18-23) (Claims 8, 9 & 24).

Though Atala et al teach using a retroviral vector to transfect either the parenchymal cells or endothelial cells with vector DNA encoding for the IL-1 or IL-2 angiogenesis modulating agents, it would have been obvious to one of ordinary skill in the art to alternatively use a plasmid containing the IL-1 or IL-2 genes, as they are both art accepted means of transfecting cells (Claims 1 & 23). One of ordinary skill in the art would have been motivated to perform the transfection using a plasmid because plasmids can cross species boundaries to successfully incorporate the cDNA into the mammalian cell, and use of plasmids eliminates the step of inactivating the virus, as is required with viral vectors. One would have expected success performing the transfection using a plasmid because it is a well known and accepted method of transfection practiced in the art and Atala et al teach any accepted form of transfection is acceptable in their method (See, e.g., Yla et al, Pg. 213-214; See Atala et al col. 10, ln 16-22).

Atala et al teach using three-dimensional matrices derived from decellularized tissues; however it also would have been obvious to one of ordinary skill in the art at the time the invention was made to alternatively use three-dimensional matrices made from polymers such as polylactic acids or polyglycolic acids or combinations thereof (PLAs, PGAs, or PLGAs), such as those described by Cima et al (See Cima Pg. 145, col. 1) (Claims 10 & 26). One of ordinary skill in the art would have been motivated to use a polymeric matrix because Cima et al teach they are biocompatible, degradable, and processable; they are capable of allowing vasculogenesis, in the case of organ construction, and come pre-made in a variety of shapes, sizes, and are available in a variety of resorptive rates (See Cima et al, Pg. 145, col. 1). One would have expected success because Cima et al teach successfully using polymeric matrices to develop cartilage constructs for transplantation as well as liver constructs for transplantation.

Griffith-Cima et al provide another alternative to decellularized tissue in US Patent 5,709,854, where they disclose a matrix comprised of hydrogel, in which cells can be cultured and then subsequently injected into a patient to form an organ equivalent or tissue construct (See col. 1, ln 27-58). Therefore one of ordinary skill in the art would have been motivated to use a matrix comprised of hydrogel in the method of Atala et al in place of decellularized tissue (Claim 25). One of ordinary skill in the art would have been motivated to use an injectable hydrogel matrix to avoid surgical implantation and pre-shaping/manipulation of the matrix, as is required with solid matrices. Additionally, Griffith-Cima et al teach the hydrogel is biocompatible, biodegradable, and can successfully be used to deliver large amounts of cells into a patient. One would have expected success because Griffith-Cima et al teach successfully forming cartilaginous structures using chondrocyte populations embedded in hydrogel; therefore one would expect similar success with any cell type, including the transfected populations of the method of Atala et al.

Claims 1, 3-9, 23, 24 and 27-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Atala et al (US Patent 6,479,064), in view of Yla et al (Lancet, 2000), further in view of Lee et al (Circulation, 2000).

Atala et al teach a method of augmenting organ function comprising culturing a population of endothelial cells on a three-dimensional matrix to form an organ construct capable of differentiation *in vivo* to replace or augment organ function; and seeding a second population of parenchymal cells onto the matrix; and co-administering the cell populations by implanting the organ construct *in vivo* at a target site to induce assimilation and differentiation of cells in the target region (See col. 2, ln 19-52; col. 12, ln 37-49; and Claims 1 & 14) (Claims 1, 5, 23 and 29). Atala et al teach the endothelial cells to form a primitive vascular system, therefore it appears Atala et al intends to use vascular endothelial cells (See col. 2, ln 19-52) (Claims 4 and 7); the parenchymal cells can comprise undifferentiated muscle stem cells

(See col. 9, ln 7-19) (Claims 3 and 6). Atala et al teach either the endothelial cells or the parenchymal cells can be transfected, by any means known in the art, to produce a gene product beneficial for transplantation, such as angiogenesis modulating agents IL-1 or IL-2 (See Specification, Pg. 3; See Atala et al col. 10, ln 4-23 & col. 14, ln 24-30). The three-dimensional matrix can be implanted into the subject, therefore it acts as a pharmaceutically acceptable carrier; it can comprise decellularized tissue, it can further be treated with collagen or other materials to aid in cellular attachment and growth (See col. 11, ln 30-38 & col. 12, ln 18-23) (Claims 8, 9 & 24).

Though Atala et al teach using a retroviral vector to transfect either the parenchymal cells or endothelial cells with vector DNA encoding for the IL-1 or IL-2 angiogenesis modulating agents, it would have been obvious to one of ordinary skill in the art to alternatively use a plasmid containing the IL-1 or IL-2 genes, as they are both art accepted means of transfecting cells (Claims 1 & 23). One of ordinary skill in the art would have been motivated to perform the transfection using a plasmid because plasmids can cross species boundaries to successfully incorporate the cDNA into the mammalian cell, and use of plasmids eliminates the step of inactivating the virus, as is required with viral vectors. One would have expected success performing the transfection using a plasmid because it is a well known and accepted method of transfection practiced in the art and Atala et al teach any accepted form of transfection is acceptable in their method (See, e.g., Yla et al, Pg. 213-214; See Atala et al col. 10, ln 16-22).

Atala et al teach a general method of forming an organ construct comprising culturing two different cell types on a single matrix, intending for implantation into a subject; however they are relatively general on the types of cell that can be used, teaching that endothelial cells and parenchymal cells are preferred embodiments. Lee et al teach a method of transfecting primary murine myoblasts with a VEGF gene, and then implanting the transfected cells, into the ventricular wall of SCID mice in order to induce angiogenesis at the site of implantation (See pg. 899, col. 1). It would have been obvious to one of ordinary skill in the art at the time the invention was made to form a construct, such as done by Atala et

al, using the transfected myoblasts of Lee et al (Claims 27 and 38). One of ordinary skill in the art would have been motivated to use transfected myoblasts as the parenchymal cells in the construct of Atala et al in order to form a muscle construct for implantation, such as for a replacement heart valve, or to strengthen the walls of the heart muscle. Myoblasts are undifferentiated muscle cells, therefore when seeded in a matrix with vascular endothelial cells the construct could be implanted into a patient to augment heart or other muscle function. One would expect success because Lee et al teach the transfected myoblast cells expressed the VEGF and induced assimilation and differentiation of the cells in the implantation region and would induce vasculogenesis of the construct (See Pg. 889, col 2, and abstract).

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1, 3 and 8-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Springer et al (J Gene Med, 2000), in view of Yla et al (Lancet, 2000), further in view of Lanza et al (US Patent 5,891,477).

Applicant's claim 1 is directed to a method of organ augmentation comprising the steps of: transfecting a population of cells with a plasmid encoding an angiogenesis modulating agent; and implanting the transfected cells into a target tissue region where the cells will express the angiogenesis modulating agent thereby inducing assimilation and differentiation of cells in the target region. Claim 3 requires the population of cells to comprise undifferentiated cells. Claim 8 requires the cells to be suspended in a pharmaceutically acceptable carrier. Claim 9 requires the pharmaceutically acceptable carrier to comprise collagen. Claim 10 requires the pharmaceutically acceptable carrier to comprise a polymer matrix. Claim 11 requires the step of transfecting the cells to further comprise selecting stably

transfected cells. Claim 12 requires the populations of cells to comprise myoblasts. Claim 13 requires the angiogenesis modulating agent to be VEGF.

Springer et al teach transfecting a population of primary myoblasts with a retrovirus containing a VEGF gene, implanting the primary myoblasts stably expressing VEGF within alginate microcapsules coated with poly-L-lysine (which applicant calls a pharmaceutically acceptable carrier comprising a polymer matrix), and implanting the microcapsules under the skin and in the peritoneal cavity of SCID C.B-17 mice (See Springer et al, Pg. 280) (Claims 1, 8 and 10-13). Primary myoblasts are undifferentiated muscle cells (Claim 3). The cells expressed the VEGF and induced assimilation and differentiation of the cells in the implantation region; however overproduction of the VEGF caused hemorrhaging and tumor growth in the regions under the skin, and caused hemoperitoneum, enlargement of the spleen and tumors in the peritoneal cavity (See Pg. 281, col. 2 & pg 283, col. 1).

Though Springer et al uses a retrovirus to transfect the myoblast cells with the VEGF cDNA, it would have been obvious to one of ordinary skill in the art to alternatively use a plasmid containing the VEGF cDNA, as they are both art accepted means of transfecting cells (Claim 1). One of ordinary skill in the art would have been motivated to perform the transfection using a plasmid because plasmids can cross species boundaries to successfully incorporate the cDNA into the mammalian cell, and use of plasmids eliminates the step of inactivating the virus, as is required with viral vectors. One would have expected success performing the transfection using a plasmid because it is a well known and accepted method of transfection practiced in the art (See, e.g., Yla et al, Pg. 213-214).

While Springer et al teaches use of a simple microcapsule comprised of alginate and poly-L-lysine, Lanza et al provides a more comprehensive list of suitable microcapsules that may be used as pharmaceutically acceptable carriers. Lanza et al teach a preferred microcapsule substantially similar to that used by Springer; the preferred microcapsule contains a cell or tissue that is the source of a therapeutic substance, the microcapsule can include a hydrogel member, such as alginate, and a semi-

permeable membrane or coating, such as a polymer matrix, in particular polylysine (See col. 3, ln 7- 27). Lanza et al also teach the microcapsule can optionally comprise collagen, to allows for alteration of the size of the pores in the gel matrix (See col. 14, ln 12-28) (Claim 9). Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use alternative microcapsules, such as those described by Lanza et al, in the method of Springer et al. One of ordinary skill in the art would have been motivated to use the different microcapsules described by Lanza et al, especially the one comprising collagen, because Lanza et al teach that the addition of collage allows for manipulation of the pore size of the matrix, so as to influence transport properties. One would expect success using a variety of different microcapsules, such as those described by Lanza et al because Lanza et al teach the microcapsules are intended to house cells, including myoblasts, in order to secrete therapeutic substances, such as VEGF, after implantation into a subject (See, e.g. col. 24, ln 53-63). Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1, 3 and 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (Circulation, 2000), in view of Yla et al, (Lancet, 2000).

Applicant's claim 1 is directed to a method of organ augmentation comprising the steps of: transfecting a population of cells with a plasmid encoding an angiogenesis modulating agent; and implanting the transfected cells into a target tissue region where the cells will express the angiogenesis modulating agent thereby inducing assimilation and differentiation of cells in the target region. Claim 3 requires the population of cells to comprise undifferentiated cells. Claim 11 requires the step of transfecting the cells to further comprise selecting stably transfected cells. Claim 12 requires the populations of cells to comprise myoblasts. Claim 13 requires the angiogenesis modulating agent to be VEGF.

Lee et al teach implanting primary murine myoblasts, transfected by a retrovirus with a murine VEGF gene, into the ventricular wall of SCID mice (See pg. 899, col. 1) (Claims 1, 12 and 13). Myoblasts are undifferentiated muscle cells (Claim 3). The cells expressed the VEGF and induced assimilation and differentiation of the cells in the implantation region; however overproduction of the VEGF caused hemangiomas and death (See Pg. 889, col 2, and abstract).

Though Lee et al does not specifically state stably transfected cells were chosen for implantation, it appears as if all cells transplanted were initially determined to be stably transfected. It would have been obvious to one of ordinary skill in the art at the time the invention was made to select only stably transfected cells for transplantation. One of ordinary skill in the art would have been motivated to select stable transfected cells as a routine matter of optimization, so as to not introduce additional variables. It is commonly known in the art to control all variables; therefore the population of transfected cells would be expected to be homogenously stable. Methods of selecting stably transfected cells would be known to one of ordinary skill in the art, therefore one would expect success choosing a stably transfected cell population (Claim 11).

Though Lee et al uses a retrovirus to transfect the myoblast cells with the VEGF cDNA, it would have been obvious to one of ordinary skill in the art to alternatively use a plasmid containing the VEGF cDNA, as they are both art accepted means of transfecting cells (Claim 1). One of ordinary skill in the art would have been motivated to perform the transfection using a plasmid because plasmids can cross species boundaries to successfully incorporate the cDNA into the mammalian cell, and use of plasmids eliminates the step of inactivating the virus, as is required with viral vectors. One would have expected success performing the transfection using a plasmid because it is a well known and accepted method of transfection practiced in the art (See, e.g., Yla et al, Pg. 213-214). Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1, 3 and 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Springer et al (Molecular Cell, 1998), in view of Yla et al, (Lancet, 2000).

Applicant's claim 1 is directed to a method of organ augmentation comprising the steps of: transfecting a population of cells with a plasmid encoding an angiogenesis modulating agent; and implanting the transfected cells into a target tissue region where the cells will express the angiogenesis modulating agent thereby inducing assimilation and differentiation of cells in the target region. Claim 3 requires the population of cells to comprise undifferentiated cells. Claim 11 requires the step of transfecting the cells to further comprise selecting stably transfected cells. Claim 12 requires the populations of cells to comprise myoblasts. Claim 13 requires the angiogenesis modulating agent to be VEGF.

Springer et al teach transfecting a population of myoblasts with a retrovirus containing a murine $VEGF_{164}$ cDNA. The transfected cells were then implanted in the leg muscles of recipient mice where the cells expressed the VEGF protein (See pg. 549, col. 2) (Claims 1, 12 and 13). Myoblasts are undifferentiated muscle cells (Claim 3). The cells expressed the VEGF and induced assimilation and differentiation of the cells in the implantation region; however overproduction of the VEGF caused hemangiomas containing localized networks of vascular channels and other deleterious effects.

Though Springer et al does not specifically state stably transfected cells were chosen for implantation, it appears as if all cells transplanted were initially determined to be stably transfected. It would have been obvious to one of ordinary skill in the art at the time the invention was made to select only stably transfected cells for transplantation. One of ordinary skill in the art would have been motivated to select stable transfected cells as a routine matter of optimization, so as to not introduce additional variables. It is commonly known in the art to control all variables; therefore the population of transfected cells would be expected to be homogenously stable. Methods of selecting stably transfected

cells would be known to one of ordinary skill in the art, therefore one would expect success choosing a stably transfected cell population (Claim 11).

Though Springer et al uses a retrovirus to transfect the myoblast cells with the VEGF cDNA, it would have been obvious to one of ordinary skill in the art to alternatively use a plasmid containing the VEGF cDNA, as they are both art accepted means of transfecting cells (Claim 1). One of ordinary skill in the art would have been motivated to perform the transfection using a plasmid because plasmids can cross species boundaries to successfully incorporate the cDNA into the mammalian cell, and use of plasmids eliminates the step of inactivating the virus, as is required with viral vectors. One would have expected success performing the transfection using a plasmid because it is a well known and accepted method of transfection practiced in the art (See, e.g., Yla et al, Pg. 213-214). Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1, 2 and 13 are rejected under 35 U.S.C. 103(a) as being anticipated by Lazarous et al (Cardiovascular Research, 1999), in view of Yla et al (Lancet, 2000).

Applicant's claim 1 is directed to a method of organ augmentation comprising the steps of: transfecting a population of cells with a plasmid encoding an angiogenesis modulating agent; and implanting the transfected cells into a target tissue region where the cells will express the angiogenesis modulating agent thereby inducing assimilation and differentiation of cells in the target region. Claim 2 requires the step of transfecting the cells to further comprise transiently transfecting the cells, such that the angiogenesis modulating agent is produced for less than three weeks. Claim 13 requires the angiogenesis modulating agent to be VEGF.

Lazarous et al teach a method of organ augmentation comprising the steps of: transfecting cells of canine pericardium using an adenovirus that encoded for human $VEGF_{165}$, a known angiogenesis

modulating agent; the transfection was performed *in vivo* by transcutaneous injection by way of a pericardial catheter (See Pg. 296, col. 1) (Claims 1 & 13). The measurable increase in VEGF expression lasted for only 14 days (See Pg. 297, col. 2 & Fig. 3) (Claim 2).

Though Lazarous et al perform the transfection *in vivo*, it would have been obvious to one of ordinary skill in the art at the time the invention was made to alternatively perform the transfection *ex vivo*, using either heterologous cells for transfection, or isolating autologous cells from the subject for transfection and then re-implanting the cells after transfection. One of ordinary skill in the art would have been motivated to perform the transfection *ex-vivo* and then re-implant the transfected cells into the patient in order to ensure only properly transfected cells were re-implanted, to minimize the area of cells exposed to the adenovirus by not injecting the adenovirus solution into the patient, which would allow for possible secretion and migration; or if heterologous cells were used for the transfection, invasiveness of the treatment would be greatly minimized. One would have expected success performing the transfection *ex vivo* because the cells are exposed to the same transfection vectors, and Lazarous et al confirmed the expression of the human VEGF on canine vascular endothelial cells *in vitro* prior to performing the *in vivo* transfection, therefore they taught the transfection can successfully be performed *in vitro*.

Additionally, though Lazarous et al use an adenovirus encoding the VEGF gene to transfect the cells, it would have been obvious to one of ordinary skill in the art at the time the invention was made to alternatively use a plasmid encoding the same gene to transfect the cells. Current technique in molecular biology recognize the use of both viral vector and plasmid vector transfection as generally equivalent methods (See, e.g. Yla et al, Pg. 213-214); additionally, applicant provides in their specification acknowledgement of the use of an adenoviral vector as a preferred embodiment for transiently transfecting cells for the claimed method (See Specification, Pg 73). Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1, 3 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isner et al (WO 98/19712).

Applicant's claim 1 is directed to a method of organ augmentation comprising the steps of: transfecting a population of cells with a plasmid encoding an angiogenesis modulating agent; and implanting the transfected cells into a target tissue region where the cells will express the angiogenesis modulating agent thereby inducing assimilation and differentiation of cells in the target region. Claim 3 requires the population of cells to comprise undifferentiated cells. Claim 13 requires the angiogenesis modulating agent to be VEGF.

Isner et al teach a method of modulating angiogenesis comprising transplanting endothelial progenitor cell modified to express an endothelial cell mitogen (See Pg. 5, ln 5-12 and Pg. 14, ln 6-11) (Claims 1 and 3). Isner et al teach endothelial cell mitogens to include acidic and basic fibroblast factors, vascular endothelial growth factor, epidermal growth factor, transforming growth factor alpha and beta, platelet derived endothelial growth factor, platelet derived growth factor, tumor necrosis factor alpha, hepatocyte growth factor, insulin like growth factor, erythropoietin, colony stimulating factor, macrophage-CSF, granulocyte/macrophage CSF, and nitric oxidesyntase (See Pg. 16, ln 23- Pg. 17, ln 10) (Claim 13).

Though Isner et al do not teach specific steps of transfecting the endothelial progenitor cells to express the endothelial cell mitogens, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use a suitable plasmid encoding for the appropriate gene to transfect the endothelial progenitor cells of interest. One of ordinary skill in the art would have been motivated to perform transfection using a plasmid vector and would have expected success because the use of plasmid vectors for gene therapy is a well known and accepted method in the art (See, e.g. Yla et al). Therefore, the method of Isner et al, modified in view of Yla et al to use plasmid vectors to transfect the endothelial

cells, teach the same method as in the current application, and thus the method of Isner et al, in view of Yla et al, is one and the same as the method for augmenting organ function, as in the current application. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 5, 8, 10, 23-26 and 29 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 11, 16, 17 & 18 of copending Application No. 10/292,166. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of co-pending application '166 do not require one of the populations of cells to be transfected with a plasmid encoding an angiogenesis modulating agent as is required by the current application. However, the claims of the current application fall into the scope claimed by co-pending application '166 as the current claims are directed to a method for augmenting organ function comprising: perfusing at least one population of cultured cells on or into a matrix material, such that cells attach to the matrix material; culturing the cells in the matrix material to produce a tissue layer capable of differentiating into an artificial organ construct, thereby producing a three-dimensional biomatrix; and implanting the three dimensional biomatrix into at least one target site in the organ, such

that the tissue layer of the three dimensional biomatrix differentiates to provide a gain of function to the organ, thereby augmenting organ function at the target site (co-pending application claim 11, current claims 1, 5, 8, 23 and 29); wherein the matrix is decellularized tissue (co-pending application claim 16; current claims 24), hydrogel (co-pending application claim 17; current claim 25), or a polymer (co-pending application claim 18; current claims 10 and 26). Thus it would have been obvious to one of ordinary skill in the art to first transfect one of the populations of cells with a plasmid encoding an angiogenesis modulating agent, making the current claims obvious over the claimed method of '166. One of ordinary skill in the art would have been motivated to first transfect a population of cells with a plasmid encoding for an angiogenesis modulating agent in order to increase the expression of the angiogenesis modulating agent in the construct formed by the present methods. One would have expected success because it is well known in the art that transfecting a cell, or population of cells, with a plasmid encoding an angiogenesis modulating agent would successfully result in increased expression of the transfected DNA.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Allison M Ford whose telephone number is 571-272-2936. The examiner can normally be reached on M-F 7:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Allison M Ford
Examiner
Art Unit 1651

LEON B. LANKFORD, JR.
PRIMARY EXAMINER